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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,037	01/19/2005	Klaus Michael Debatin	085449-0152	6277

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

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11/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,037	DEBATIN ET AL.	
	Examiner	Art Unit	
	HONG SANG	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-43 and 45-52* is/are pending in the application.

4a) Of the above claim(s) *35-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Debatin et al.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/16/2009 has been entered.

2. Claims 35-43 and 45-52 are pending. Claims 1-34 and 44 have been cancelled. Claims 35-43 have been withdrawn from consideration. Claim 46 has been amended.

3. Claims 45-52 are under examination.

Rejection Withdrawn

4. The rejection of claims 45-52 under 35 U.S.C. 103(a) as being unpatentable over Alnemri (WO 02/16418A2, Pub. Date: 2/28/2002, IDS), in view of Wang (WO 02/16402, Pub. Date: 2/28/2002, IDS), and Ford et al. (Gene Therapy, 2001, 8: 1-4) is withdrawn in view of new grounds of rejection.

New grounds of Rejection

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 45-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alnemri (WO 02/16418A2, Pub. Date: 2/28/2002, IDS), in view of Wang (WO 02/16402, Pub. Date: 2/28/2002, IDS), Carson et al. (Cancer Res., 2002, Jan, 63:18-23, IDS), Ford et al. (Gene Therapy, 2001, 8: 1-4), and Trouet et al. (US 2004/0014652A1, Pub. Date: 1/22/2004, effective filing date: 6/1/2000, earlier pub. date (PCT/EP01/ 06106): 12/6/2001)

Alnemri discloses that Smac, a mitochondrial protein, which is released together with cytochrome c from the mitochondria in response to apoptotic stimuli, was found to promote caspase activation by binding and neutralizing the IAPs (see page 4, last paragraph). Alnemri teaches a composition for inducing cancer cell apoptosis comprising an isolated Smac peptide or polypeptide comprising the residue 56-139 of SEQ ID NO.1, and a physiologically acceptable carrier (see page 6, lines 3-6, the paragraph bridging pages 6-7, page 18, lines 1-2, page 37, claims 52, 53 and 88). Alnemri teaches mature Smac that is a Smac polypeptide without the 55 amino acid residue mitochondrial targeting sequence (MTS) (see page 12, lines 9-11), the first 7 residues of mature Smac, Smac-N7, SEQ ID NO.6 and the first 35 residues of mature Smac, Smac-N35, SEQ ID NO.11 (see the paragraph bridging pages 46-47). Alnemri

teaches that short peptides derived from the N-terminus of mature Smac (e.g. Smac-N7, and Smac-N35) could be used as promoters of caspase enzymatic activity at attainable concentrations to kill cancer cells that overexpress IAPs (see the paragraph bridging pages 46-47). Alnemri teaches that the Smac peptides or polypeptides are human Smac (see page 41, Example 1).

Alnemri does not teach a Smac peptide or polypeptide that is linked to the TAT protein, or an amino acid domain 37-72 or 47-57 of the TAT protein via a chemical bond. Alnemri does not teach that the composition of the Smac polypeptide further comprises a cytostatic compound such as doxorubicin. However, these deficiencies are made up for in the teachings of Wang and Ford et al.

Wang et al. teach a pharmaceutical composition for inducing cancer cell apoptosis comprising a therapeutically effective amount of the AV peptide, and further comprising an additional therapeutic agent such as an anti-neoproliferative chemotherapeutic agent, and a pharmaceutical acceptable carrier (see page 3, lines 1st -3rd paragraph, page 14, 2nd paragraph, page 18, claims 1-8), wherein the AV peptoid is the residue 56-59, 56-60, 56-61, 56-62 of the full length Smac protein (see page 28, Table).

Carson et al. disclose that translocation of Smac from mitochondria to cytosol was observed in LNCaP cells that undergo apoptosis (see abstract). Carson et al. teach microinjection of Smac and cytochrome c into the cytoplasm of prostate cancer LNCaP (see page 20). Carson et al. teach that the presence of Smac in the cytosol

made LNCaP cells sensitive to cytochrome c-induced apoptosis (see page 20, column 2).

Ford et al. teach that large molecules (β-galactosidase, horseradish peroxidase etc), when chemically cross-linked with TAT peptides (either amino acids 1-72 or 37-72) were taken up by cells in vitro and in vivo (see page 2, 2nd column). Ford et al. disclose that the still smaller TAT protein basic domain (37-47 amino acids) rapidly translocated through the plasma membrane and accumulated in the nucleus (see page 2, 2nd column). Ford et al. disclose efficient cellular uptake of a small peptide conjugated to the TAT peptide (see page 2, 2nd column). Ford et al. teach that TAT-mediated delivery can be improved by constructing fusion proteins between several polypeptides and proteins and the 47-57 region of the TAT protein (see page 2, 2nd column). Ford et al. disclose that denatured TAT protein as well as regions of the TAT protein have shown to be able to efficiently transport proteins and peptides into cells (see page 2, column 2). Ford et al. disclose that many proteins have been successfully transported into a wide variety of human and murine cell types using the TAT PTD methodology (see page 2, column 2, paragraph 2). Ford et al. expressly state that protein transduction may also enable more efficient penetration and delivery at solid tumor sites (see page 3, column 1, last paragraph).

Trouet et al. teach a biologically active entity (construct) comprising an intracellularly active entity linked to a transport peptide, wherein the intracellularly active entity is cytotoxic or cytostatic toward cell and exerts its cytotoxic or cytostatic activity within the cell (see page 11, paragraph [0119]). Trouet et al. teach that these

intracellular active entities may or may not be able to penetrate the cells by themselves, and can be small molecules, peptide, and proteins (see page 11, paragraph [0120]). Trouet et al. teach that the transport peptide portion of the construct enables, facilitates or enhances transport of the intracellularly active entity into the target cell and/or nuclear translocation of the entity (see page 11, paragraph [0120]). Trouet et al. teach that the transport peptide portion of the construct can be a TAT peptide, and exogenous Tat protein translocates through the plasma membrane and reaches the cell nucleus (see page 11, paragraphs [0123] and [0125]). Trouet et al. teach use of tumor-selective transport peptide (e.g. Tat) for intracellular delivery of doxorubicin (see Example 9). Trouet al. teach that pro-apoptotic protein-transport peptide constructs such as granzyme B-transport peptide construct can be administered alone or in combination with doxorubicin(see page 12, paragraphs [0137] and [0143]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to chemically link the Smac peptide or polypeptide taught by Alnemri or Wang to the TAT protein or the 37-72 or 47-57 residue of the TAT protein for purpose of delivering the Smac peptide or polypeptide into the cytoplasm or even the nucleus of tumor cells in view of the teachings of Carson, Ford and Trouet. One would have been motivated to do so because Smac peptides or polypeptides were known to exert its pro-apoptotic activity (promoting caspase activation) in the cytosol of tumor cells by binding and neutralizing the IAPs, and the Smac protein does not penetrate cell membrane well as shown by the teachings of Carson that Smac was microinjected into the cytoplasm of prostate cancer cell. Moreover, Ford et al. teach that proteins when

linked to the 37-72 or 47-57 residue of TAT protein can be effectively delivered into cell cytoplasm or nucleus, and Trouet et al. teach that the transport peptide portion of the construct enables, facilitates or enhances transport of the intracellularly active entity into the target cell and/or nucleus (see page 11, paragraph [0120]). One of ordinary skill in the art would have a reasonable expectation of success to chemically link the Smac protein or peptide of Alnemri or Wang to the TAT protein, or the 37-72 or 47-57 residue of TAT protein because method of making a fusion protein including proapoptotic protein-TAT fusion protein was well known in the prior art as shown by Ford and Trouet.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, one would have been motivated to include doxorubicin in the composition of Alnemri or Wang because Wang et al. teach a composition comprising a Smac peptide and a chemotherapeutic agent, and doxorubicin was used widely as a chemotherapeutic drug, and Trouet al. teach that pro-apoptotic protein-transport peptide constructs such as granzyme B-transport peptide construct can be administered alone or in combination with doxorubicin(see page 12, paragraphs [0137] and [0143]).

Response to Arugments

Applicant's arguments presented in the response filed on 2/18/2009 have been responded in the advisory action mailed 3/17/2009 and will not be repeated in this action.

Conclusion

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Hong Sang/
Examiner, Art Unit 1643